ADDISON'S DISEASE

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Until very recently the metabolic disturbances underlying the syndrome resulting from lack of function of the adrenal cortex were little understood. Knowledge in this field has been very rapidly gained in recent years so that many of the clinical manifestations are now explicable on the basis of known disturbances of metabolism.

Clinical Manifestations

The onset of Addison's disease is usually insidious, though the first obvious manifestations may occur as an acute crisis. The commonest single cause of lack of function of the adrenal cortices is their bilateral destruction by tuberculosis, this being the lesion in over 50 per cent. of cases. The other causes are 'atrophy,' amyloid disease, neoplasms, vascular lesions, pyogenic infections, while haemochromatosis and possibly syphilis are rarer factors. It seems that the importance of tuberculosis as the destructive agent is gradually decreasing and that the so-called atrophy is now almost if not more frequently found. Overall, both sexes are about equally affected but tuberculosis is the underlying agent in a greater proportion of men than women (Guttman, 1930). The disease is most often seen between the ages of 30 and 50; it is uncommon, being seen once in 6,000 hospital patients (Rowntree and Snell, 1931). When, as is usual, the onset of the disease is chronic, the following are the cardinal groups of symptoms, in order of frequency.

1. *Asthenia.* Muscular weakness, persistent or recurrent, is always present. It may not be so noticeable when the patient first gets up in the morning but, as the day draws on, the patient begins to feel weaker and finds that the slightest exertion causes intense muscular fatigue. In addition, lightheadedness and faintness may be noticed, particularly when the patient has been lying down and suddenly sits or stands up.

2. *Loss of Weight.* This invariably occurs and a diagnosis of Addison's disease in its absence will almost invariably be wrong. The patient need not necessarily be underweight for his height, the important manifestation being weight *loss*.

3. *Increasing Melanotic Pigmentation.* About 95 per cent. of patients exhibit this manifestation, which is frequently the most striking. Indeed the remarks of friends about the patient's colour may, on the one hand, be the first factor leading the patient to seek medical advice or, on the other hand, they may cause the listless and wasting patient to postpone his visit, since melanotic pigmentation is so fashionably associated with physical fitness.

The increased pigmentation is most obvious and marked in patients who are normally dark and occurs also in those areas which are normally pigmented. Thus, the face and neck, axillae, nipples and areolae, and ano-genital regions become more deeply pigmented than they were previously, and moles and freckles become more obvious. In addition increased pigmentation becomes obvious in areas which are frequently subjected to pressure, such as the elbows, or in women who wear corsets, in the epigastrium. The creases in the palms of the hands and over the knuckles may also show pigmentation and, important from the diagnostic point of view, the buccal and vaginal mucosae usually show pigmented patches. Oral pigmentation, however, can occur unassociated with any racial characteristic, with haemochromatosis or with Addison's disease—the three conditions usually considered in the differential diagnosis.

Scars arising from wounds inflicted before the onset of the Addison's disease tend to remain unpigmented, but those occurring during the course of the disease are usually fringed with brown pigment. In addition to the above findings the hair may become noticably darker and in about 10 per cent. of cases vitiligo occurs with hyperpigmentation round the depigmented areas. Guttman (1930) found in his survey that the duration of the disease was very much longer in patients in whom the first manifestation was increasing pigmentation, than in those where the onset of pigmentation more or less coincided with other symptoms. A considerable number of such chronic cases are reported in the literature where the pigmentation ante-dated all other manifestations of Addison's disease by many years (Sorkin, 1949).

4. *Gastro-intestinal Manifestations.* About 90 per cent. of patients show some gastro-intestinal disturbances, the most frequent being anorexia. This is usually persistent and may gradually increase in intensity and is frequently associated with spells of vomiting and attacks of abdominal pain lasting for a few days at a time. Attacks of diarrhoea may also occur which sometimes alternate with constipation. Until other manifestations have suggested the correct diagnosis, patients may be suspected of having peptic ulcer, 'chronic appendicitis,' 'chronic cholecystitis' or other even more vague alimentary pathology. Occasionally, a craving for salt may occur, but this is unusual and should not be relied upon as a diagnostic sign.

5. *Hypoglycaemic Manifestations.* In the more severe cases attacks of spontaneous hypoglycaemia may occur (Thorn, Koeff, Lewis and Olsen, 1940). These usually occur in the early hours of the morning or at other times of the day where a considerable period has elapsed without the intake of food, particularly if an unusual amount of exercise has been taken. The manifestations may occur at blood sugar levels of 50 or 60 mg. per 100 ml. which are not usually associated with symptoms in normal subjects. These symptoms are the same as occur with hypoglycaemia in non-Addisonian subjects and vary from a feeling of hunger and weakness, perhaps with sweating and trembling, to epileptiform convulsions, or to deep coma with gross abnormalities of the central nervous system.

6. *Psychiatric Disturbances.* Frequently, mental disturbances in Addisonian patients are so mild as to escape notice unless one is aware that they might occur. The most usual features are inability to concentrate, lack of memory and sometimes emotional instability. The most important feature about these disturbances of mental function is, however, that they are often the first signs of an impending Addisonian crisis; they should be regarded as such if they appear as a new feature in an Addisonian who has been apparently progressing satisfactorily under treatment with DOCA and/or salt.

The intellectual deterioration which may occur is well illustrated by a recently seen patient who normally had a taste for good literature. Whenever his treatment was inadequate he resorted to reading strip-cartoons.

7. *Prostration after Minor Injury.* It is frequently found that patients with Addison's disease become very ill from minor infections or from relatively trivial trauma such, for example, as dental extractions. At times it is this feature which gives the clue to the underlying nature of the disease.

8. *Muscular Cramps.* These are complained of by about a sixth of Addisonian patients. Very rarely muscular paralysis may occur, the result of a high extracellular potassium concentration, accentuated by a low concentration sodium.

On physical examination the most striking features are the evidence of loss of weight, a small and feeble pulse associated with a low blood pressure, pigmentation, the features of which have already been described, and diminished growth of bodily hair, particularly in the axillae where it may be almost or totally absent. Sometimes obvious signs of pulmonary tuberculosis are present and occasionally tenderness in the lumbo-costal angle may be found, a sign described by Rogoff (1931). Thorn, Forsham and Emerson (1951) also describe stiffness of the pinnae, the result of sclerotic changes which take place in the cartilage.

X-ray of the chest, which should be carried out in every case in order to determine whether pulmonary tuberculosis is present, shows that the heart is abnormally small; in those cases resulting from tuberculosis destruction of the suprarenals, calcification of these glands may be seen on the appropriate X-ray.

The electrocardiogram is not infrequently abnormal, the characteristic findings being prolonged PR or QT intervals, low-voltage ventricular complexes, low or inverted T waves and slight depression of the RT segment. (Thorn, Dorrance, and Day, 1942.) According to Sorkin (1949) these changes are more frequently found after prolonged treatment with DOCA and indeed may only appear after such treatment.

Abnormalities in the electroencephalogram have been described (Hoffman, Lewis and Thorn (1942) and Engle and Margolin (1942)) but there seems to be no definite conclusion yet as to their precise causation.

Adrenal Crisis

There are at least three distinct types of acute episodes which may occur in Addison's disease.

1. *Hypoglycaemia.* This has already been mentioned, but it is worth emphasizing that it may be sudden in onset and very profound. This is exemplified by a case seen recently where DOCA had been implanted one afternoon into an Addisonian patient who had had the disease for several years. He was found unconscious when breakfast was taken the following morning and physical examination showed him to be deeply in coma and that a hemiplegia had developed. The blood sugar was found to be 20 mg. per 100 ml. Recovery only occurred after several days although the blood sugar was controlled by intravenous administration and cortisone was given.

2. *Acute Circulatory collapse.* (True adrenal crisis.) The onset of this may be very sudden or may occur over a period of a day or so. Prodromal symptoms such as general malaise or some mental disturbances may occur and these are followed by nausea and vomiting with abdominal pain or discomfort. Dehydration rapidly occurs, the pulse becomes fast and thready and the blood pressure falls to low levels. The temperature is usually sub-normal, but hyperpyrexia may sometimes occur. If the condition progresses the patient becomes delirious, lapses into coma and dies.

This acute collapse is one of the most serious abnormalities occurring in Addison's disease and tends to occur after trauma, which may be slight, or during infections. As has already been mentioned it is important to recognize that mental symptoms may be the first feature of an impending crisis.

3. *Hyperpotassaemia with Muscular Paralysis.* This is a very rare occurrence in Addison's disease but it is mentioned separately, since a case has been seen recently, and since it is not unlikely that similar cases have been seen in the past without being recognized. Over a period of hours there is a gradual increase in muscular weakness which culminates in a complete flaccid paralysis. Profound changes in the electrocardiogram also occur and ventricular fibrillation may be the terminal event. In the case mentioned, the serum potassium was 9.75 mEq/litre (38 mg. per 100 ml.) (Richardson and Sibley, 1952).

Laboratory Findings

Electrolyte Abnormalities. The characteristic electrolyte abnormalities found in untreated Addison's disease are a low concentration of sodium and of chloride in the serum together with a high concentration of potassium. Unfortunately, these findings are by no means constantly present and cases entering fatal crisis have been described where the electrolyte values were normal (Loeb, Atchley and Parsons (1937)).

The deficiency in sodium results in a decrease in extra-cellular fluid volume and in circulatory plasma volume. The defective renal circulation leads to defective excretion of urea, the blood concentration of which rises. One would expect the poor plasma volume to be reflected in a high haematocrit level, but there is frequently a certain degree of anaemia so that the resultant haematocrit is often about normal.

Water regulation by the kidney is also abnormal in Addison's disease, there being no diuresis in the first few hours after the ingestion of a water load.

These abnormalities in electrolyte and water metabolism form the basis of two tests for adrenocortical function, the Robinson-Kepler-Power (1941) water test and the Cutler-Power-Wilder (1938) test.

The former is not very reliable, being frequently negative in cases of Addison's disease and positive wherever there is serious sodium depletion. The latter consists of giving a high-potassium-low-sodium diet for many days thus unveiling the inefficient electrolyte regulation; whilst more reliable than the Robinson-Kepler-Power test it is unpleasant to the patient and there is a very real danger of precipitating an adrenal crisis. There is now less need for either of these tests as diagnostic procedures and therefore they will not be described in detail.

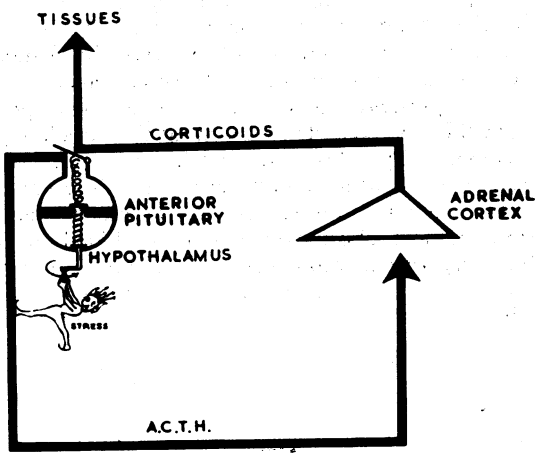
It has recently been shown that the Na/K ratio in sweat (Conn and Louis, 1950 and Locke, Talbot, Jones and Worcester, 1951) and in saliva (Frawley and Thorn, 1951) is abnormally high in Addison's disease. The collection of sweat is rather elaborate for a routine test but the salivary ratio, being carried out on saliva secreted before breakfast, is relatively simple and may form a useful diagnostic test.

Abnormalities in Carbohydrate Metabolism. The occurrence of spontaneous hypoglycaemia has already been mentioned, and as would be expected, a low fasting blood glucose level is frequently found in Addison's disease. In addition, however, the oral glucose tolerance tends to be of the ' flat ' type and there is a tendency for the blood sugar to fall to well below the fasting level 2-3 hours after the test dose of glucose. Patients with Addison's disease are also abnormally sensitive to insulin.

Haematological Abnormalities. De la Balze, Reifenstein and Albright (1946) have shown that the percentage of lymphocytes in the peripheral blood tends to be higher than normal in Addison's disease. It is unusual for the total white count to be very high and, as pointed out by Thorn *et al.* (1951), if a known case of Addison's disease is found to have a lower lymphocyte percentage than one would expect (20 per cent. in the example given) it is highly suggestive of an infective process.

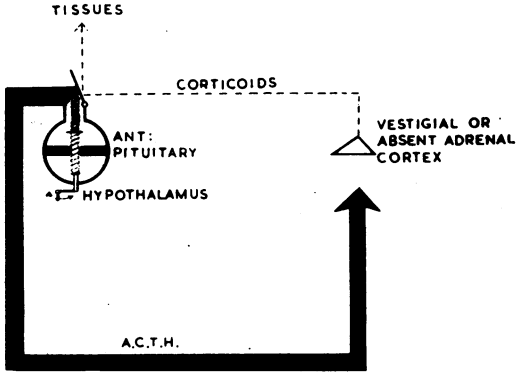
The eosinophil count is never very low in Addison's disease and usually tends to run in the upper normal range, although occasional cases do show abnormally high levels.

The haemo-concentration mentioned above would give rise, one would expect, to high haematocrit values and to high levels of haemoglobin. In untreated cases of Addison's disease the values are frequently found to be normal, since there is a deficiency in red blood cell formation; when treatment is given the haematocrit and haemoglobin fall and these estimations are often followed carefully in order to evaluate the effect of therapy.



ANTERIOR PITUITARY — ADRENOCORTICAL RELATIONSHIP NORMAL

FIG. 1.—Diagrammatic representation of inter-relationship of anterior pituitary and adrenal cortex under normal conditions. The output of ACTH has an inverse relationship to the blood level of corticoids. Sayers and Sayers (1947) think that "stress" causes the tissues to utilize greater amounts of corticoids, so lowering the blood level and causing an increased output of ACTH. The arrangement shown is more in accord with clinical facts and there is direct evidence that "stress" acts on the anterior pituitary by way of the hypothalamus and causes increased output of ACTH.



PROBABLE ANTERIOR PITUITARY-ADRENOCORTICAL RELATIONSHIP IN ADDISON'S DISEASE

FIG. 2.—Probable relationship of anterior pituitary and adrenal cortex in Addison's disease. Proof will depend upon adequate methods of estimating blood levels of ACTH. Such methods are being developed, but there are as yet no reports of the levels found in suitable numbers of untreated patients with Addison's disease.

The Underlying Physiological Disturbances

Some 26 steroid compounds have been isolated from extracts of the adrenal cortex and, in addition, a biologically potent amorphous residue is found, the contents of which have not been identified. Biologically, the substances produced have a variety of actions, the most important of which, for the purposes of the present discussion, are sodium-potassium regulating, carbohydrate-regulating-stress-resisting and protein anabolic. It is emphasized that it is quite possible for a single steroid to possess all of these effects in varying degrees, the position is by no means fully understood and is complicated by the fact that interconversion of one steroid to another may occur in the body. With this in mind, the functional classification is very useful and the physiological disturbances will be discussed on this basis.

Figs. 1 and 2 are diagrammatic, greatly simplified, representations of the inter-relationships of the anterior pituitary and adrenal cortex in health and in Addison's disease. The hormones, particularly the carbohydrate-regulating hormones, or glucocorticoids, produced by the adrenal cortex as a result of ACTH stimulation cause a depression of ACTH production and a balance is achieved by this sort of biological servo mechanism. Sayers and Sayers (1947) believe that under conditions of stress the tissues utilize more of the glucocorticoids thereby lowering the level circulating in the blood. As a result, more ACTH is released from the anterior pituitary and this stimulates greater glucocorticoid production by the adrenal cortex. It is difficult to see how this theory accords with all the facts, since during conditions of stress, increased quantities of glucocorticoid-like substances are found in the urine, and since the ingestion of cortisone or hydrocortisone by mouth, without stress, causes the tissues to react in a similar way as they do to a stressful stimulus. At all events it can be seen that in Addison's disease, where there is destruction of the adrenal cortical tissue, there is likely to be (1) evidence of deficiency of the various adreno-cortical hormones, (2) a great increase in circulating ACTH, and (3) no adrenal response to injected ACTH. The deficiency of the glucocorticoids probably contribute to some of the asthenia, to the spontaneous hypoglycaemia and to the severe effects of minor trauma and infection. The inevitable absence of low eosinophil counts and the relatively great lymphocyte percentage also result from this deficiency. It is probable also that cerebral metabolism is altered so producing the psychological disturbances which have been described.

Lack of 17-ketosteroids or protein anabolic hormones is shown mainly by a lack of axillary hair; the muscle wasting is also probably partly

due to this deficiency. The probability that lack of these hormones does not contribute a lot to the essential clinicial picture of Addison's disease is suggested by the occurrence of many of the features of Addison's disease in some patients with the adreno-genital syndrome due to adreno-cortical hyperplasia. In this condition, virilization is produced by the excessive quantities of 17-ketosteroids produced by the adrenal cortices, presumably sometimes at the expense of the other hormones.

Lack of the Na-K regulating hormones results in the low body sodium and high potassium with consequent extracellular dehydration and probable intra-cellular over-hydration. The resultant low circulating blood volume results in the hypotension and in the retention of urea. Also, as has been pointed out by Marriott (1947), sodium deficiency with resultant extra-cellular dehydration gives rise to anorexia and vomiting and this is probably, partly at least, the cause of the gastric symptoms in Addison's disease as well as of the muscular cramps. Very rarely the potassium retention results in sufficiently high levels of extracellular potassium to produce muscular paralysis.

There is no satisfactory explanation for the increased pigmentation which occurs in Addison's disease. It has been found that injections of commercial ACTH tends to produce pigmentation and it has been found that, during the purification of ACTH, Intermedin, the melanophore hormone derived from the pars intermedia, is closely associated with the ACTH until the final steps. This might suggest that the pigmentation results from the increased pituitary secretion which probably occurs when the adrenal cortex is destroyed. It has been emphasized by Morris (1952) that ACTH is in fact separable from a melanophore expanding hormone in vitro; nevertheless, the idea of excessive pituitary secretion is attractive and in accord with clinical observations.

Diagnosis

The diagnosis of Addison's disease is not difficult when the salient features are all present. The chief difficulties which are encountered occur (1) in those cases without pigmentation, (2) in differentiating pigmentation from causes other than Addison's disease, and (3) in mild cases where none of the clinical features, taken individually, are abnormal.

Apart from the laboratory findings described above, three tests have been devised by Thorn which specifically estimate adreno-cortical function. These all consist of stimulating the adrenal cortex and estimating the degree of response by finding (1) the change in circulating eosinophil levels, (2) the change in circulating lymphocytes, (3) the change in the urinary excretion of 17-ketosteroids and (4) in one of the tests, the change in the urinary ratio of uric acid to creatinine.

The Epinephrine Test. In its finally developed form this test consists in counting the circulating eosinophils by a direct method (the value derived from a total white blood count and differential count is not accurate enough for the purpose and is much more laborious) using venous blood taken from the patient who is kept in bed and is fasting. 0.3 cc. of 1 in 1000 solution of epinephrine is then injected subcutaneously and after 4 hours a further sample of venous blood is taken for another eosinophil count. In normal subjects the eosinophils usually fall by more than 50 per cent. whereas the change is less than this in Addisonians. This test would also be negative in hypopituitarism. It has not been found to be very reliable by the present author.

The 4-hour ACTH Test. On the morning of the test the patient is given no breakfast and three lots of 200 ml. of water are given at 2-hourly intervals. Urine is collected during the first 2-hourly period and at the end of it blood is collected for an eosinophil count. Immediately after this an amount of ACTH equivalent to 25 mg. of Armour LA-I-A (25 units) is injected intramuscularly. One hour later urine collection is again started and continued for three hours at the end of which time further blood for eosinophil counts is taken. The urinary content of uric acid and of creatinine in each of the two specimens is estimated and the ratio of these two substances in each specimen calculated. With normal adreno-cortical function the uric acid/creatinine ratio increases by 100 per cent. or more whereas Addisonians only show about a 20 per cent. increase. As in the epinephrine test, a normal subject should have a drop of 50 per cent. or more in the circulating eosinophils.

This test, though more reliable than the epinephrine test has, nevertheless, been found to be somewhat unsatisfactory by the author of this paper.

The 48-hour ACTH Test. There are a variety of procedures for carrying out this test, but a method which has been quite satisfactory is as follows. The patient is kept at rest in bed in hospital for a control period of two days during which two 24-hour specimens of urine are collected from 6 a.m. to 6 a.m. on each of the two days for 17-ketosteroid estimation. At 10 a.m. and 4 p.m. on each of these days venous blood is taken and the eosinophils counted by one of the direct methods. At 6 a.m. on the third day 25 units of ACTH are given intramuscularly and this is repeated at 6-hourly intervals for a total of

eight doses. Twenty-four-hour urine samples are again collected for 17-ketosteroid estimations and the eosinophils enumerated in samples of venous blood taken at 10 a.m. and 4 p.m. on each of the test days. If anterior pituitary hypofunction is suspected the test can, with advantage, be carried on for a further 24 hours. In Addison's disease no decrease or only a temporary decrease in eosinophils occurs during the ACTH period and there is no increase in the 24-hour output of 17-ketosteroids. The author has seen one or two cases of undoubted Addison's disease who have shown evidence of increased adreno-cortical function (a fall in eosinophils and a rise in 17-ketosteroids) during the first 12 to 24 hours but who reverted to control levels during the second 24 hours. In patients with hypopituitarism adrenocortical function becomes manifest after 36 to 48 hours of ACTH stimulation.

Treatment

The general condition of patients with Addison's disease improves immensely when steps are taken to rectify the electrolyte disturbance. In the milder cases a very high intake of sodium chloride (6-10 gm. in addition to the normal daily intake) will be sufficient to bring about a considerable improvement, but it is generally preferable to use desoxycorticosterone acetate. This is mostly destroyed in the alimentary tract when taken by mouth, and, since linguets are often unsatisfactory, it is usually administered by intramuscular injection or as pellets implanted subcutaneously.

Resting blood pressure and body weight together with a general clinical evaluation should be recorded daily and the haematocrit determined at about weekly intervals. The diet should be high in protein and carbohydrate and the meals should be small and frequent in order to lessen the possibility of hypoglycaemia. Intramuscular injections of DOCA in oil are usually started with a dose of 2.5 mg. each morning. A gain in weight should occur immediately and in its absence the dose of DOCA is increased every 48 hours by 1 mg. until a satisfactory response in weight is apparent. The dose must not be made too high however and a gain of about 1 lb. per day should be the maximum. Usually the blood pressure increases within a few days but this may take many weeks even though weight gain is satisfactory. The haematocrit rapidly falls owing to the haemodilution which occurs with the onset of treatment and the concentration of sodium, chloride, and potassium in the serum becomes normal. Excessive dosage of DOCA is manifested by the appearance of oedema, aches and pains about the joints, hypertension, headache, muscular weakness with, in extreme cases, paralysis (potassium

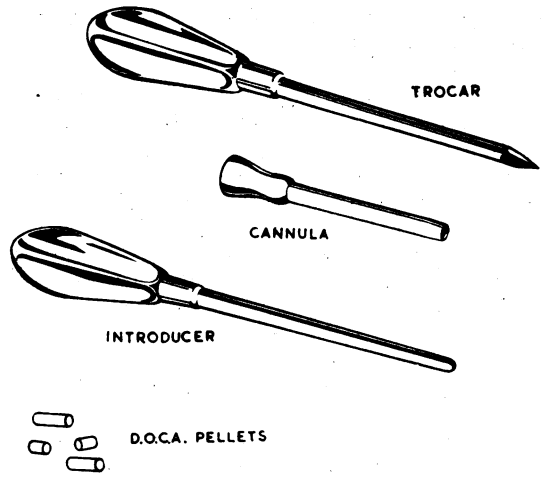


FIG. 3.—Instrument used for the implantation of DOCA pellets.

deficiency) and cardiac enlargement. The presence of any one of these features would indicate an immediate reduction in dosage.

When the correct daily dosage has been ascertained (it will not usually be more than 5 mg. per day) if the patient is doing well and seems reasonably stable, the implantations of pellets should be considered. A pellet of 100 mg. to 125 mg. is usually implanted for each 0.5 mg. of daily dose with a maximum dosage of 4 or 5 pellets (500 mg.). The process is perfectly simple if the proper introducer is used. (Fig. 3.) A small area of skin on the outer side of the thigh, on the abdominal wall or on the back below a scapula is locally anaesthetized. The trocar is placed in the cannula and the two are pushed through the anaesthetized area and then the point pushed subcutaneously, parallel with the skin, until it is about 2 inches from the entry wound. The trocar is then removed and a pellet put into the cannula and pushed beyond the end with the introducer. If more than one pellet has to be introduced, the cannula is pushed in different directions for each pellet, using the same skin wound. It is usually desirable to place one small suture in this at the end of the procedure.

These implants last six months to a year and frequently patients know subjectively when the amount of DOCA being liberated becomes too low. They can usually be instructed to increase their salt intake as required when this happens and to continue doing this until further increase becomes impracticable or until it ceases to have a beneficial effect. At this time further stabilization with DOCA and then another implant is usually necessary.

Although the above therapy is satisfactory in a number of Addisonian subjects many, although improved, never reach a state of full physical fitness, general muscular weakness, a tendency to hypoglycaemia and minor mental disturbances being the most usual features. In addition, the treatment in no way removes the possibility of adrenal crisis and hypersusceptibility to minor trauma and illness is often present. Under these circumstances the giving of appropriate amounts of glucocorticoids, whether in an adreno-cortical extract or as cortisone or Kendall's Compound F, will cause rapid improvement and a return to what seems to be normal health. The adreno-cortical extracts are very expensive and must be given by injection whereas cortisone (and Compound F) are effective by mouth and are much less expensive. The dosage required is not large, some 10 mg. to 30 mg. per day usually being sufficient. Unfortunately, however, the availability of cortisone in this country is still too meagre for its general use, even for this highly specific purpose.

American experience has shown that it is not usually possible to maintain a patient on cortisone alone, since this is insufficient to correct entirely the electrolyte abnormality. However, the concomittant dosage of DOCA is a good deal less than is required when no cortisone is given.

Fears have been expressed at the possibility of therapeutic cortisone causing a flare-up and spread of tuberculosis in those cases of Addison's disease due to this underlying condition. Although it has been shown that large doses of cortisone may result in a flare-up and spreading of tuberculosis the risk would not seem to be so great when the aim is only to restore body levels to normal.

Treatment of Adrenal Crisis

The earlier the treatment of adrenal crisis is instituted the more successful is likely to be the outcome. The treatment is also much more likely to be successful if adequate amounts of cortisone or of adreno-cortical extract are given at the earliest possible moment. Patients with Addison's disease should therefore be instructed about the early manifestations of crisis and the importance of seeking treatment at once should be emphasized. Patients who are going to any remote areas or who are going on a sea journey should take an emergency supply of cortisone or of adreno-cortical extract with them.

The following steps are recommended to combat established Addisonian crisis.

1. The patient should be kept warm in bed and general measures for shock should be instituted.
2. 30-50 ml. of aqueous adreno-cortical extract should be given intravenously.
3. 10-20 mg. of DOCA in oil should be given intramuscularly.
4. Continuous intravenous administrations of physiological saline containing 5 per cent. dextrose and 40 ml. of aqueous adreno-cortical extract per 500 ml. should be started. This should be continued, a total of about 2½ litres being given in 24 hours. Every third 500 ml. may be plasma with the adreno-cortical extract added.
5. If cortisone is available 100 mg. should be given intramuscularly at once with two further doses of 50 mg. in the first 24 hours.
6. During the second 24 hours, if improvement has occurred, 5-10 mg. DOCA and 100 mg. cortisone should be given. The intravenous therapy should be maintained, but fluids should also be given by mouth if they can be taken.
7. During the third 24 hours the dosage of DOCA may be 2.5 mg.—5 mg. and cortisone 50 mg. Intravenous therapy should be continued and feeding by mouth started if possible.
8. With sufficient improvement maintenance therapy and cessation of intravenous fluids should occur on the fourth day.
9. Penicillin and/or sulphonamides should be given as a routine since adrenal crisis is frequently initiated by an infection.
10. If hyperpyrexia occurs (over 105° F.) aspirin, 10 grains per hour, until the temperature begins to fall, may be given.
11. Morphine and allied compounds are always contra-indicated in Addison's disease.

Sometimes a severe attack of hypoglycaemia may occur in a patient adequately treated with DOCA. This should not be confused with a true adrenal crisis. The treatment consists in giving intravenous glucose preferably as a 10 per cent. solution. Provided there is an adequate flow of urine and provided the serum potassium is not elevated (where a flamephotometer is available, this can be rapidly estimated) 2 gm. of K_2HPO_4 and 0.4 gm. KH_2PO_4 can be added to each litre of the 10 per cent. glucose solution and Thorn *et al.* (1951) claim that this sometimes results in a dramatic improvement. Not more than 1000 ml. should be given in 12 hours. Intravenous glucose frequently causes pyrexia in Addisonian patients and Thorn suggests that this effect is diminished if plasma is added to the intravenous glucose solution.

100-200 mg. of cortisone should be given intramuscularly or, if this is unavailable, 50 ml. of aqueous-adreno-cortical extract should be given

intravenously and a further 100 ml. added to the glucose solution. When this is done it should not be necessary to continue the intravenous glucose beyond 24 hours.

In conclusion, it should be emphasized that there are many indications that the outlook of patients with Addison's disease has been very greatly improved by the use of cortisone. The patients feel very much better, control is much easier and the risk of crises is much diminished. A number of clinics in America are now using bilateral total adrenalectomy, with subsequent maintenance on cortisone, as a form of therapy for a variety of disorders; this adequately illustrates the facility with which adreno-cortical deficiency can be treated when adequate quantities of cortisone are available.

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